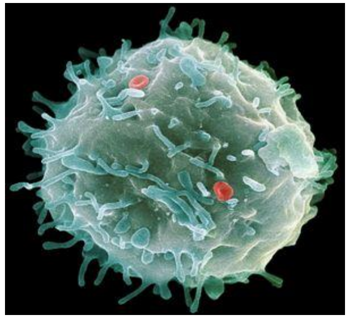
Inference of network actions for phenotypic reprogramming

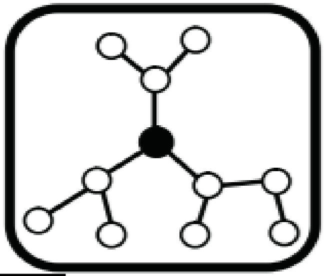
Célia BIANE, Franck DELAPLACE

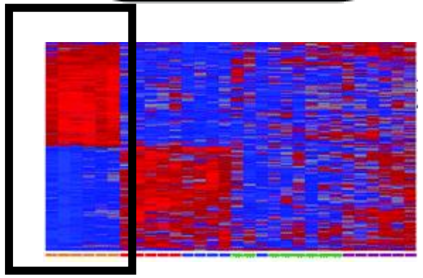
IBISC - UEVE

Causes of cellular phenotypes switches

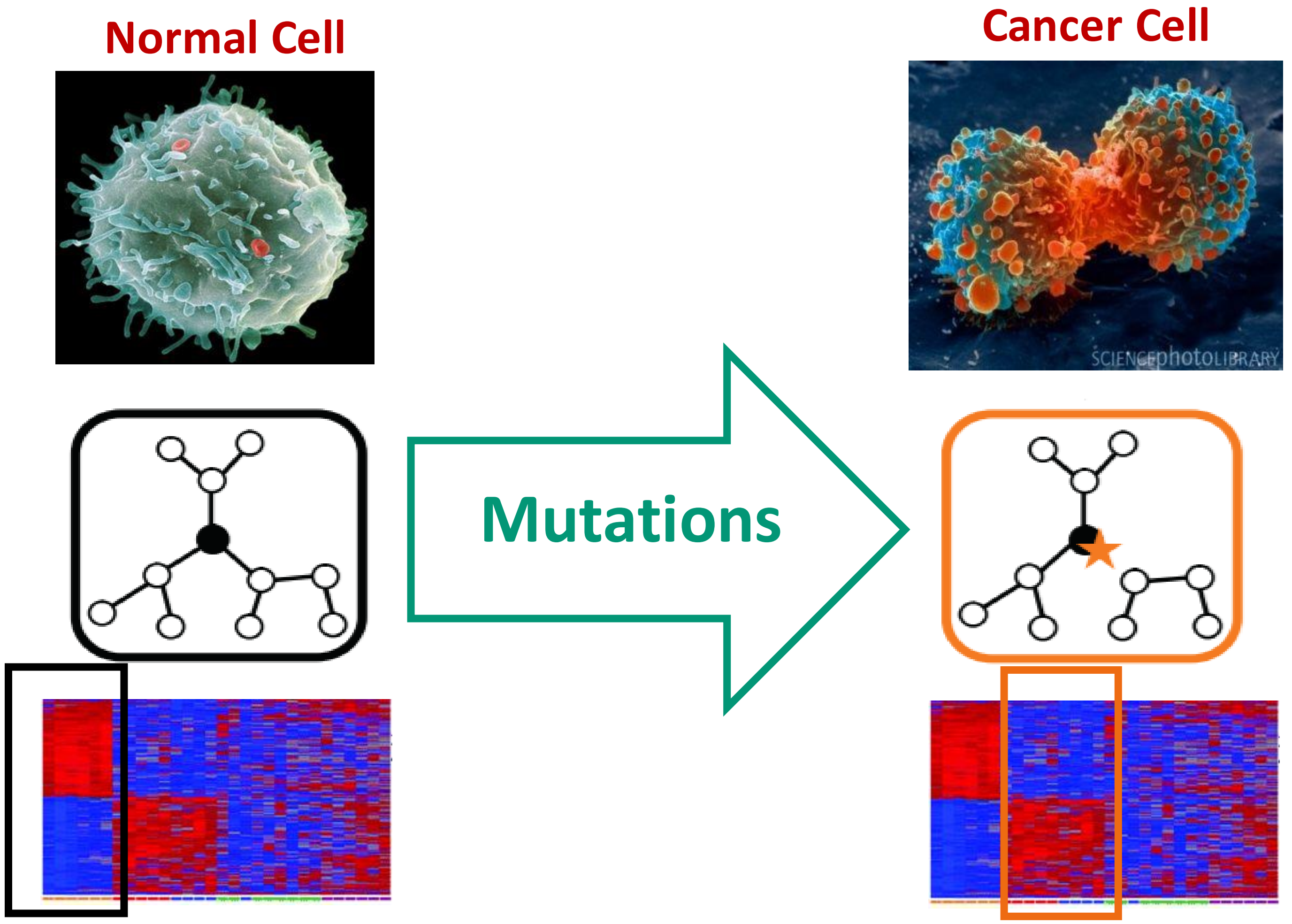
Normal Cell



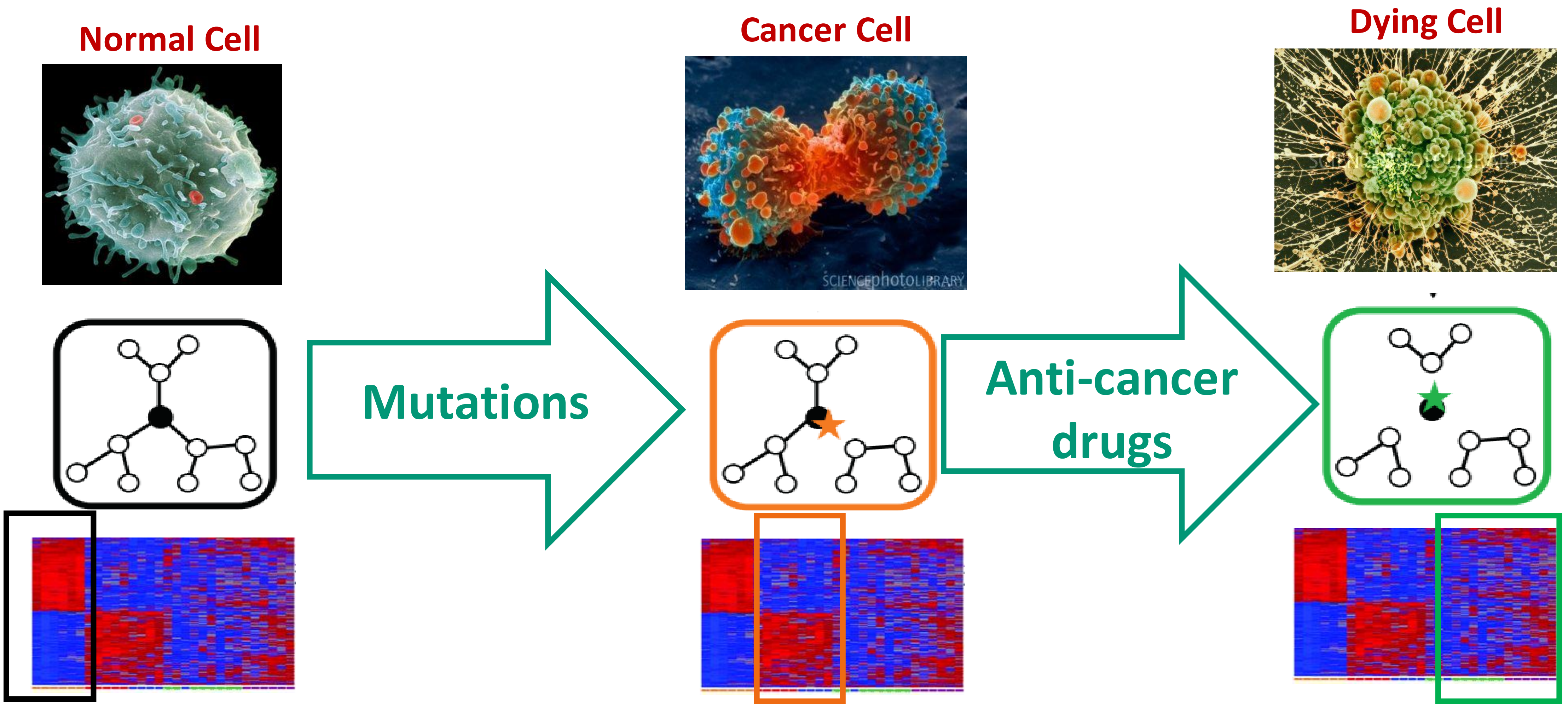




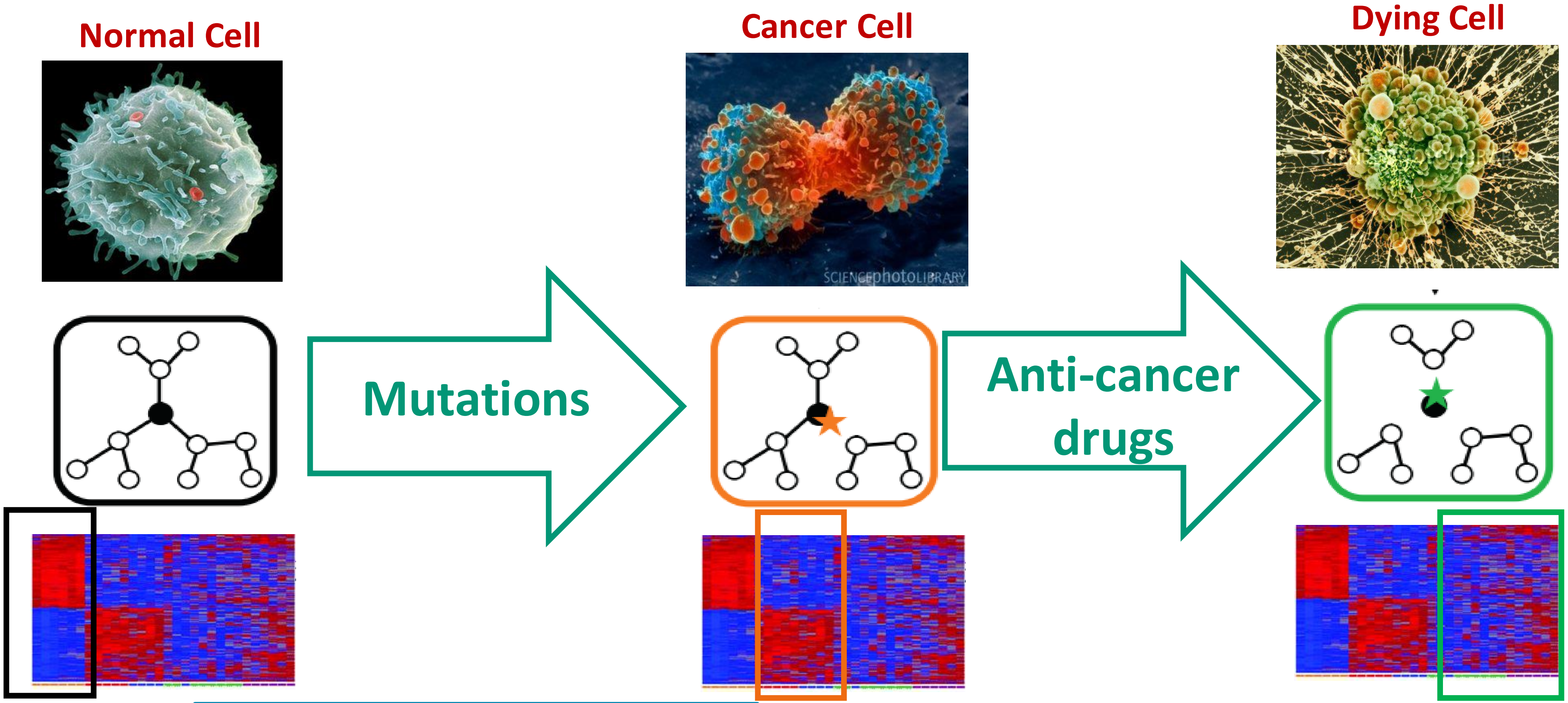
Causes of cellular phenotypes switches



Causes of cellular phenotypes switches



Causes of cellular phenotypes switches



Correlation *vs* causation

Empirical screening

→ Modelling…

Dynamical systems reprogramming

$$F = \begin{cases} x_1 = f_1(x_1, \dots, x_n) \\ \dots \\ x_i = f_i(x_1, \dots, x_n) \\ \dots \\ x_n = f_n(x_1, \dots, x_n) \end{cases}$$

Structural actions

$$G = \begin{cases} x_1 = g_1(x_1, \dots, x_n) \\ \dots \\ x_i = g_i(x_1, \dots, x_n) \\ \dots \\ x_n = g_n(x_1, \dots, x_n) \end{cases}$$

Dynamical systems reprogramming

$$F = \begin{cases} x_1 = f_1(x_1, \dots, x_n) \\ \dots \\ x_i = f_i(x_1, \dots, x_n) \\ \dots \\ x_n = f_n(x_1, \dots, x_n) \end{cases} \xrightarrow{\text{Structural actions}} G = \begin{cases} x_1 = g_1(x_1, \dots, x_n) \\ \dots \\ x_i = g_i(x_1, \dots, x_n) \\ \dots \\ x_n = g_n(x_1, \dots, x_n) \end{cases}$$

Boolean network Reprogramming

- Theoretical Framework
- Reprogramming Specification
- Inference of actions

Boolean Networks – Definition

Boolean Variables:

$$X = \{x_1, \dots, x_n\}$$

Network:

$$F = \begin{cases} x_1 = x_2 \vee x_3 \\ x_2 = \neg x_3 \\ x_3 = \neg x_2 \wedge x_1 \end{cases}$$

State:

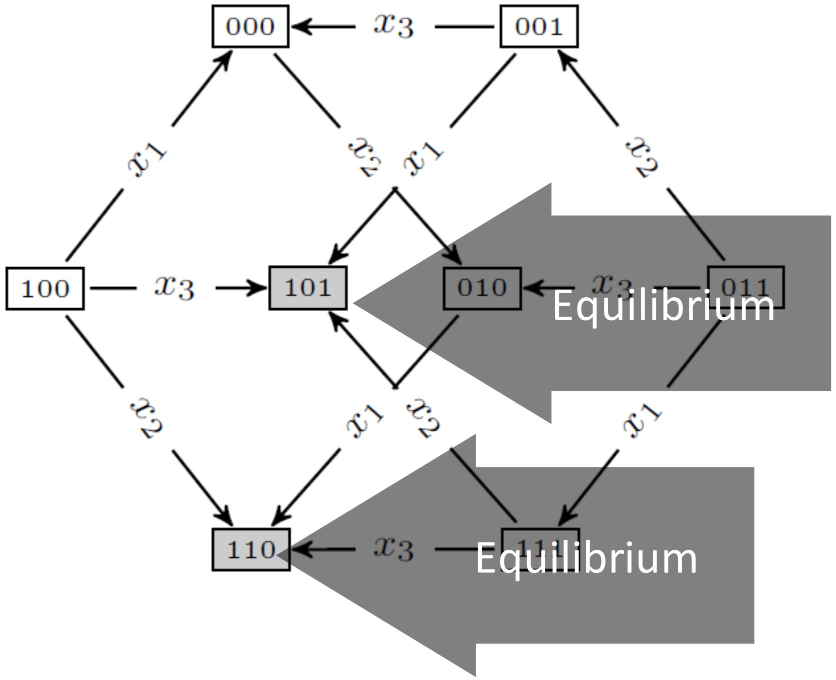
$$s : X \rightarrow \{0,1\}$$

Model of dynamics:

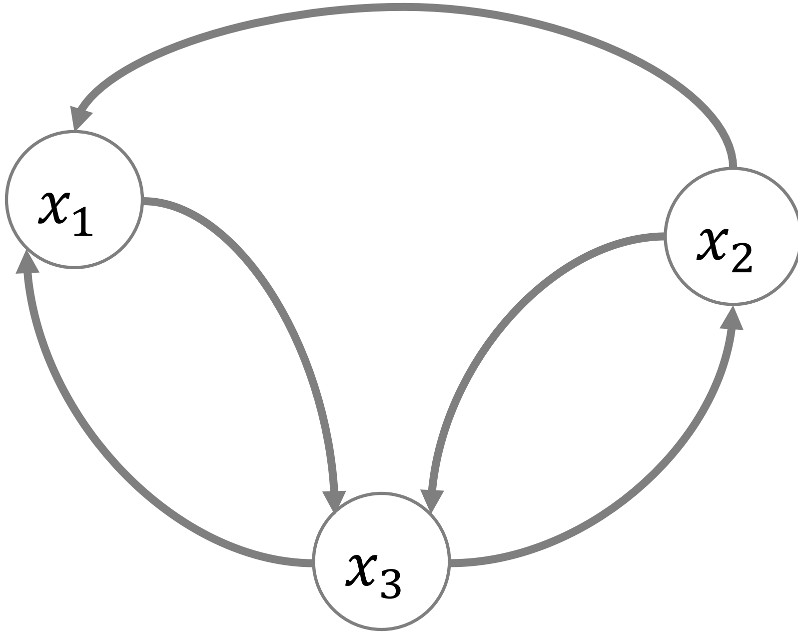
$$<\rightarrow, X, S>$$

Transition Relation:

$$\rightarrow \subseteq S \times X \times S$$



Interaction Graph:



Boolean Control networks for reprogramming

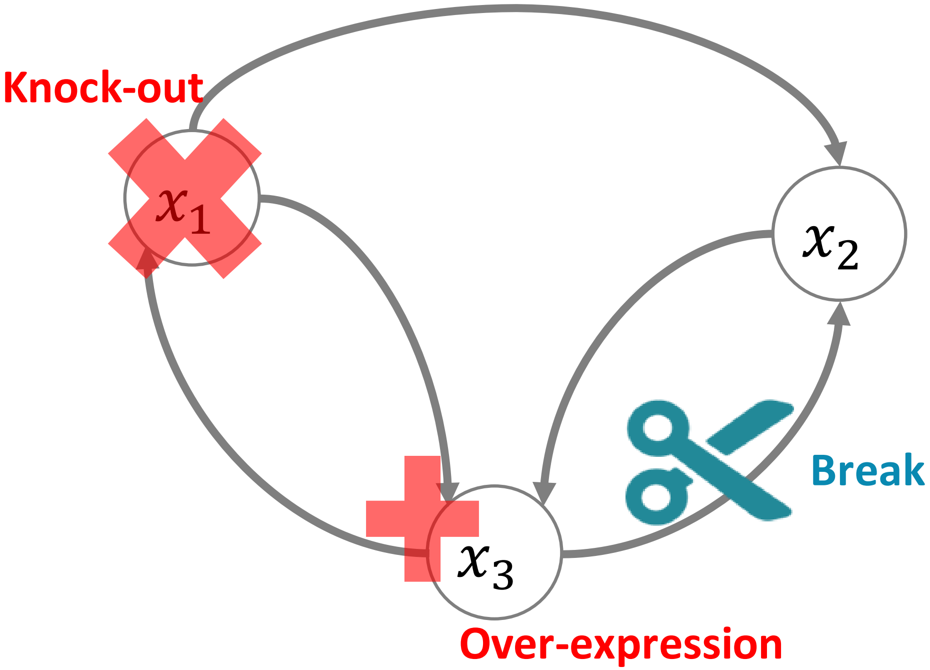
$U = \{u_1, \ldots u_m\}$: Control parameters

$$F_U = \begin{cases} x_1 = f_1(x_1, \ldots, x_n, u_1, \ldots, u_m) \\ \ldots \\ x_i = f_i(x_1, \ldots, x_n, u_1, \ldots, u_m) \\ \ldots \\ x_n = f_n(x_1, \ldots, x_n, u_1, \ldots, u_m) \end{cases}$$

Control input

$\mu : U \to \{0,1\}$

Structural control category



Convention : an active control parameter is equal to 0

Node Action: D-freezing

$$x_i = f_i(x_1, \dots, x_n) \land d_i^0$$

$$x_i = f_i(x_1, \dots, x_n) \lor \neg d_i^1$$

Edge Action: U-freezing

$$x_j = f_j\big((x_1, \dots, x_i \land u_{i,j}^0, \dots, x_n\big)$$

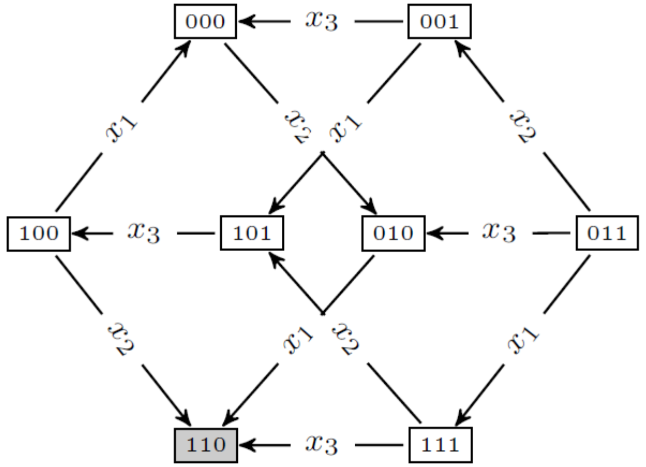
$$x_j = f_j\big((x_1, \dots, x_i \lor \neg u_{i,j}^1, \dots, x_n\big)$$

Boolean control network - Example

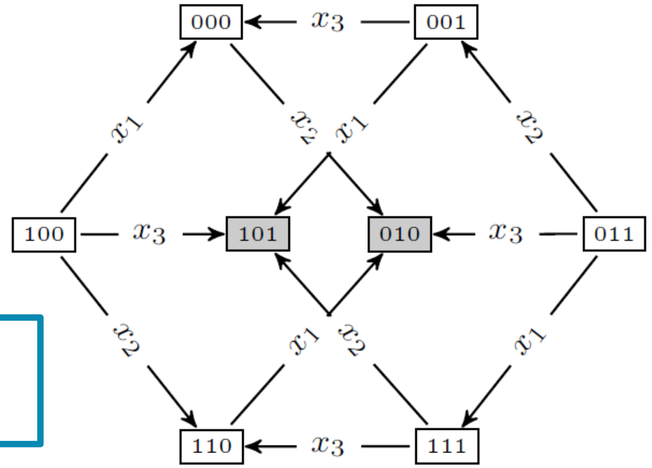
Set of control parameters U

$$F_U = \begin{cases} x_1 = (x_2 \land u^0_{2,1}) \lor x_3 \\ x_2 = \neg\left(x_3 \lor \neg u^1_{3,2}\right) \\ x_3 = \left((\neg\, x_2 \land x_1) \lor \neg d^1_3\right) \land d^0_3 \end{cases}$$

$\mu_1 = (1,1,1,0)$



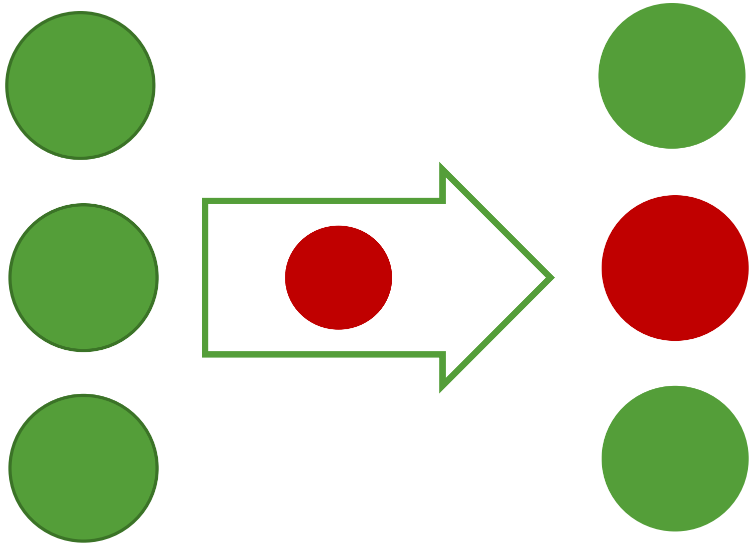
$\mu_2 = (0,1,1,1)$



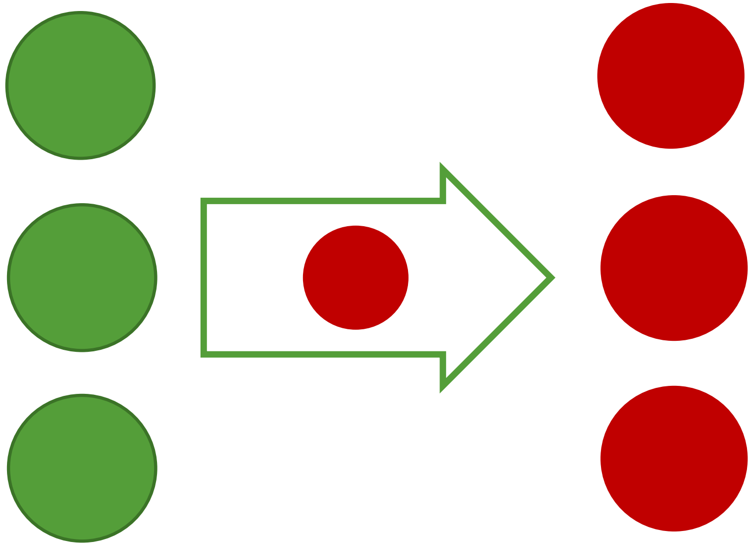
Phenotypic reprogramming specification?

Possibility/Necessity of a property

Possibility (of p)



Necessity (of p)



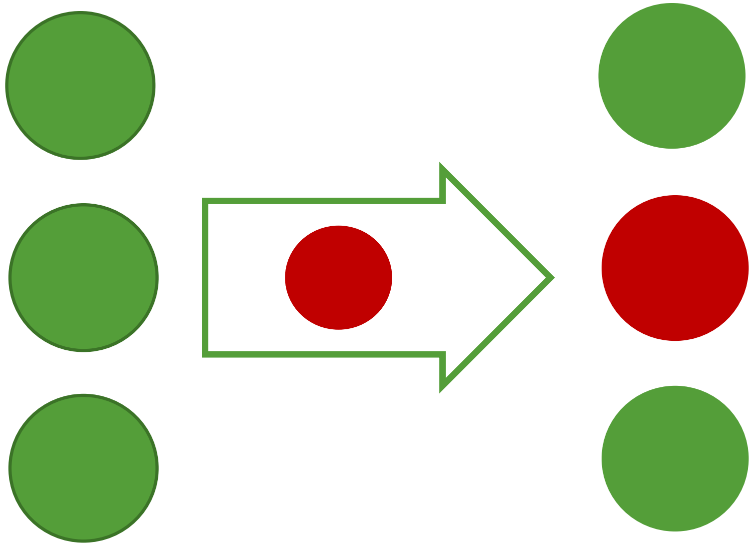
Find a control input μ such that:

$$\exists s \in S : STBL_{F_\mu}(s) \wedge p(s)$$

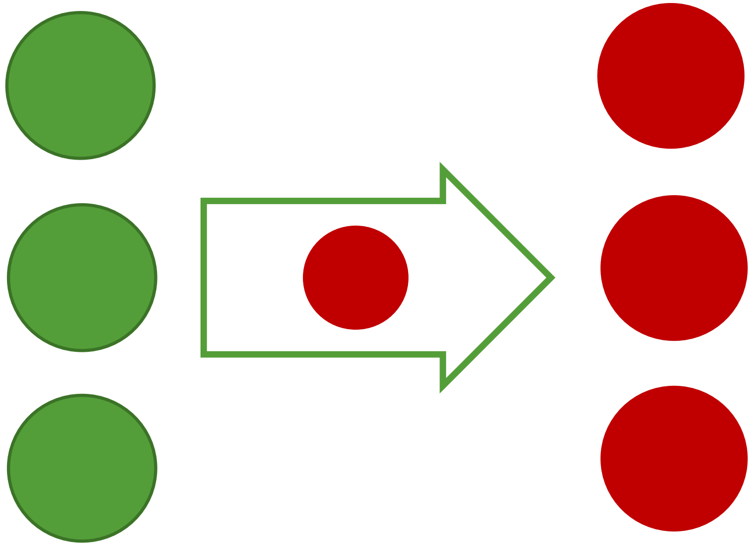
$$\forall s \in S : STBL_{F_\mu}(s) \Rightarrow p(s)$$

Possibility/Necessity of a property

Possibility (of p)



Necessity (of p)



Find a control input μ such that:

$$\exists s \in S : STBL_{F_\mu}(s) \wedge p(s)$$

$$\forall s \in S : STBL_{F_\mu}(s) \Rightarrow p(s)$$

→ Inference of μ?

Possibility and Necessity as abduction problems

THEOREM

Finding μ such that:

$$\exists s \in S : STBL_{F_\mu}(s) \wedge p(s) \qquad\qquad \forall s \in S : STBL_{F_\mu}(s) \Rightarrow \; p(s)$$

are (respectively) equivalent to finding a cube C_μ such that:

$$\left(C_s \wedge C_\mu\right) \wedge \phi \vDash STBL_{F_U} \wedge p \qquad\qquad C_\mu \wedge \phi \vDash STBL_{F_U} \Rightarrow \; p$$

where C_s, C_μ are the minterms of s, μ

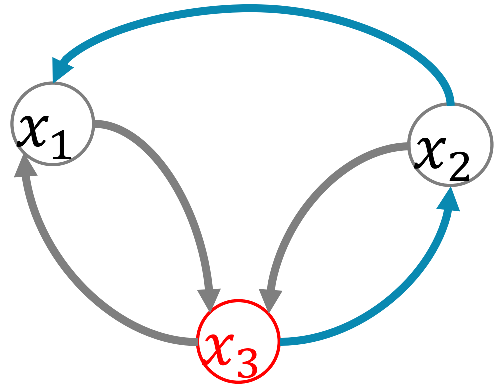
and $STBL_{F_U} \stackrel{\text{def}}{=} \bigwedge_{i=1}(x_i \Leftrightarrow f_i(x_1, \ldots, x_n, u_1, \ldots, u_m))$

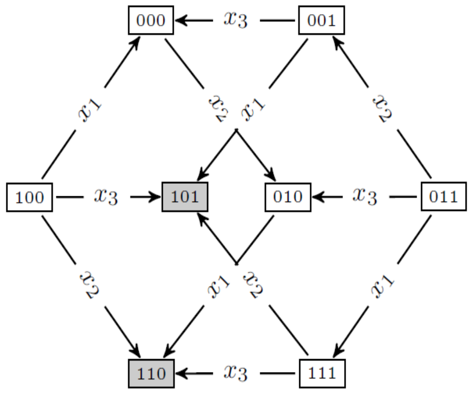
Protaxion library (Mathematica) Example

Boolean Network

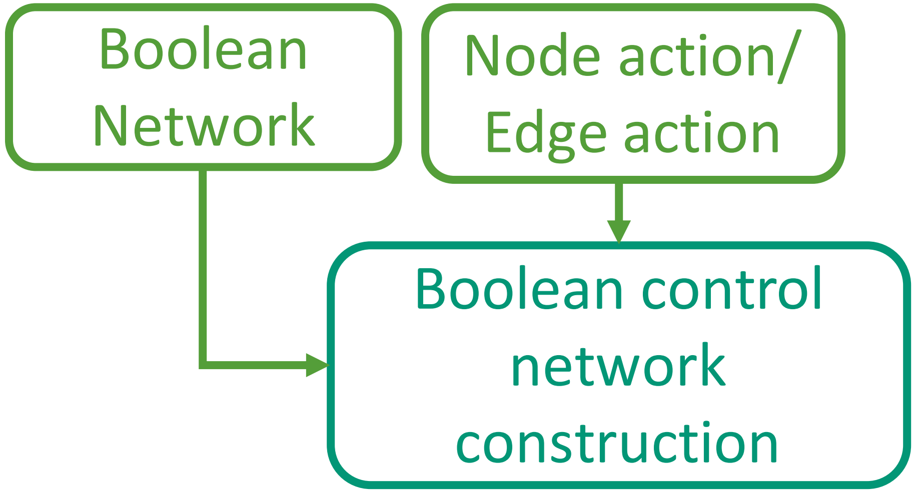
Node action/ Edge action

$$F = \begin{cases} x_1 = x_2 \lor x_3 \\ x_2 = \neg x_3 \\ x_3 = \neg\, x_2 \land x_1 \end{cases}$$

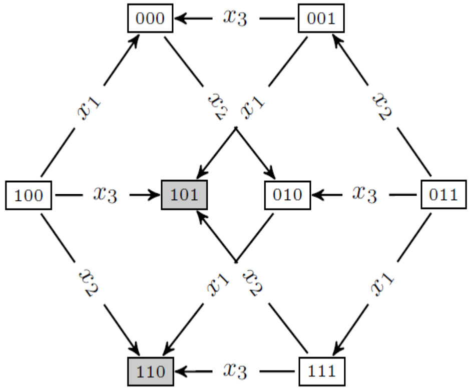


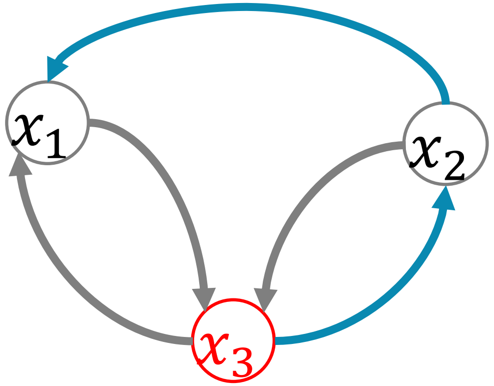


Protaxion library (Mathematica)
Example



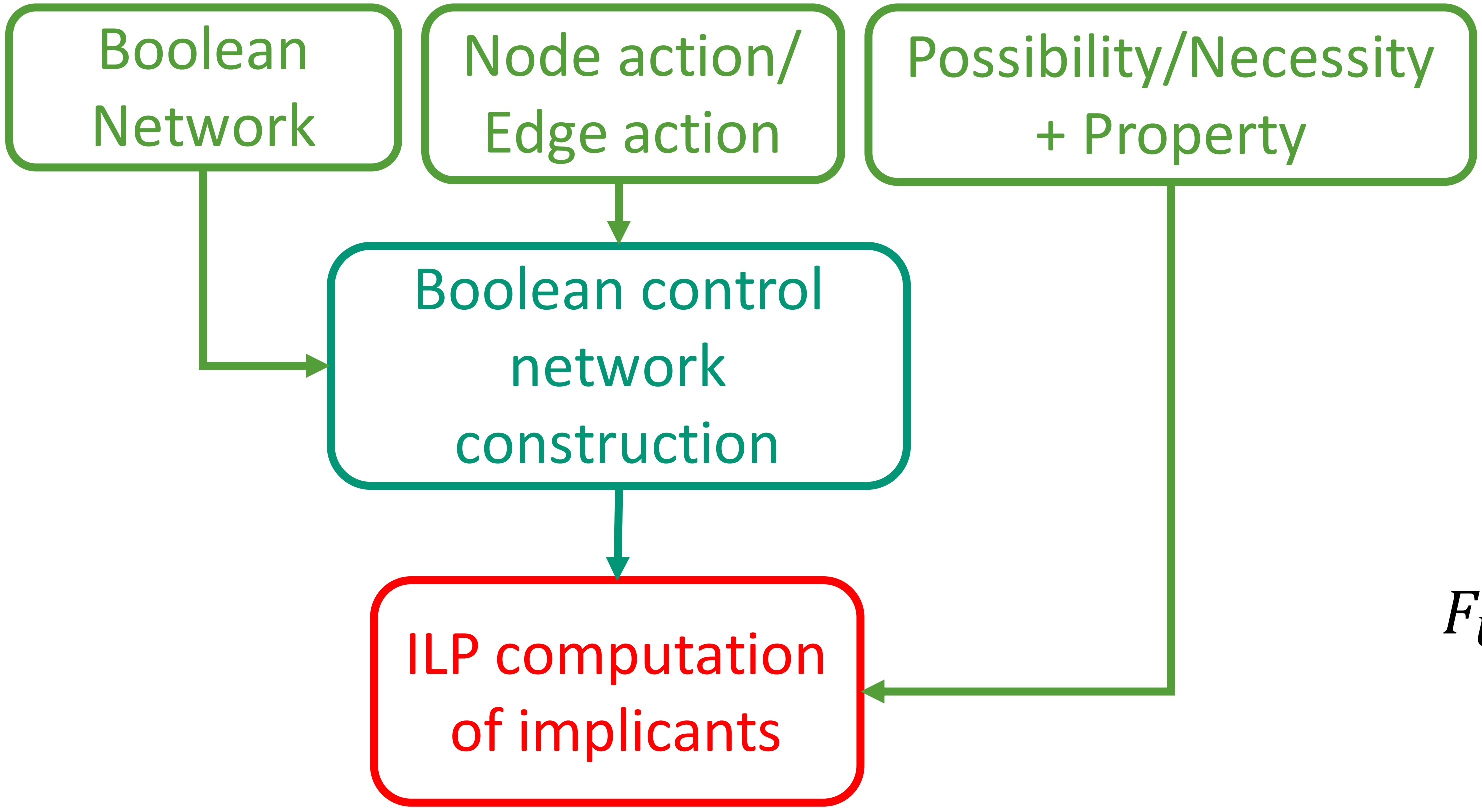
$$F = \begin{cases} x_1 = x_2 \vee x_3 \\ x_2 = \neg x_3 \\ x_3 = \neg\, x_2 \wedge x_1 \end{cases}$$



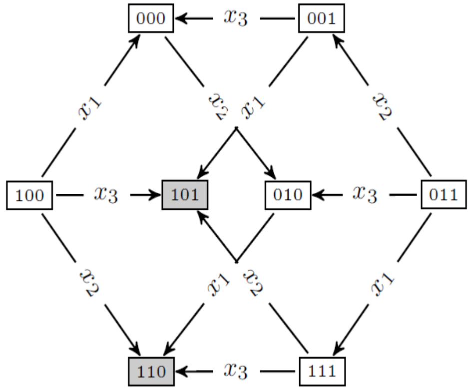


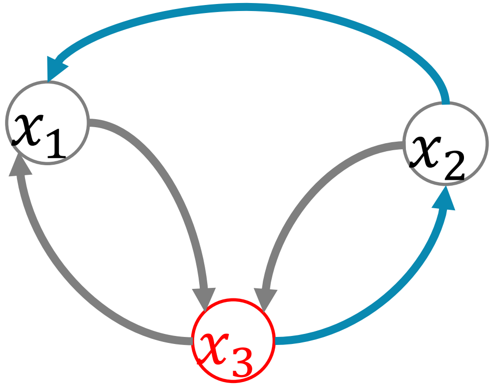
$$F_U = \begin{cases} x_1 = (x_2 \wedge u_{2,1}^{0}) \vee x_3 \\ x_2 = \neg\left(x_3 \vee \neg u_{3,2}^{1}\right) \\ x_3 = \left((\neg\, x_2 \wedge x_1) \vee \neg d_3^1\right) \wedge d_3^0 \end{cases}$$

Protaxion library (Mathematica)
Example



$$F = \begin{cases} x_1 = x_2 \lor x_3 \\ x_2 = \neg x_3 \\ x_3 = \neg\, x_2 \land x_1 \end{cases}$$

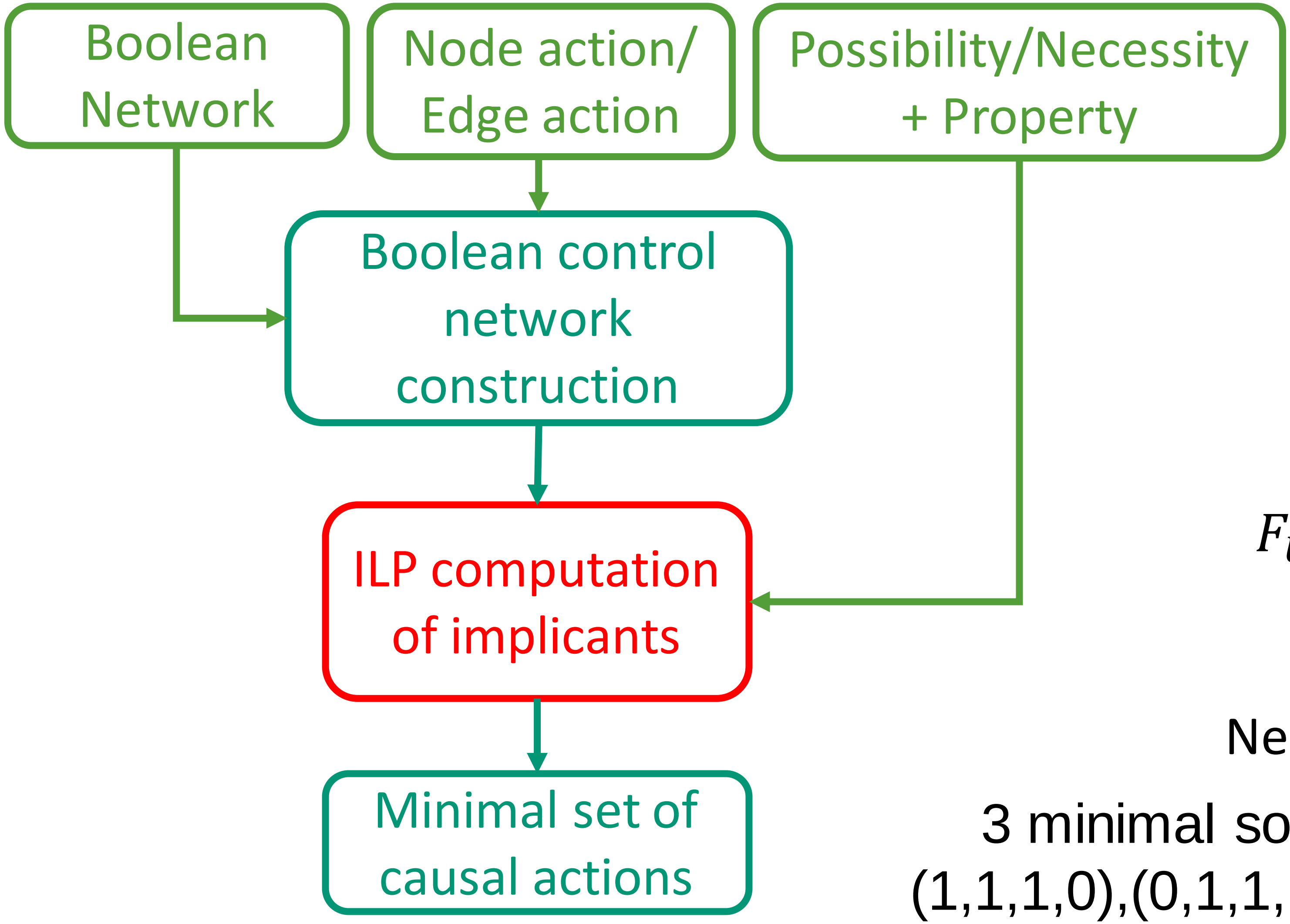




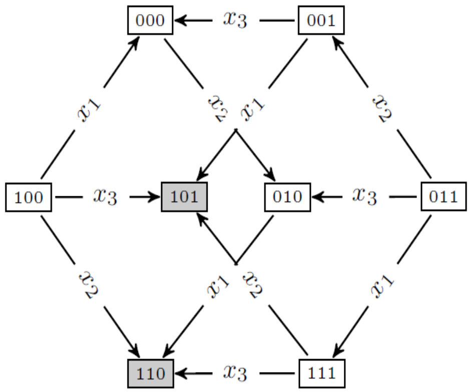
$$F_U = \begin{cases} x_1 = (x_2 \land u_{2,1}^{0}) \lor x_3 \\ x_2 = \neg\left(x_3 \lor \neg u_{3,2}^{1}\right) \\ x_3 = \left((\neg\, x_2 \land x_1) \lor \neg d_3^1\right) \land d_3^0 \end{cases}$$

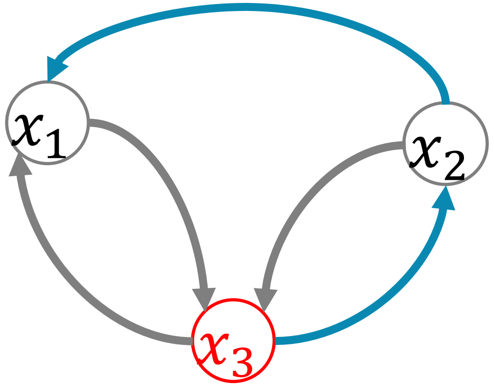
Necessary Loss of 101 stable state

Protaxion library (Mathematica) Example



$$F = \begin{cases} x_1 = x_2 \lor x_3 \\ x_2 = \neg x_3 \\ x_3 = \neg\, x_2 \land x_1 \end{cases}$$



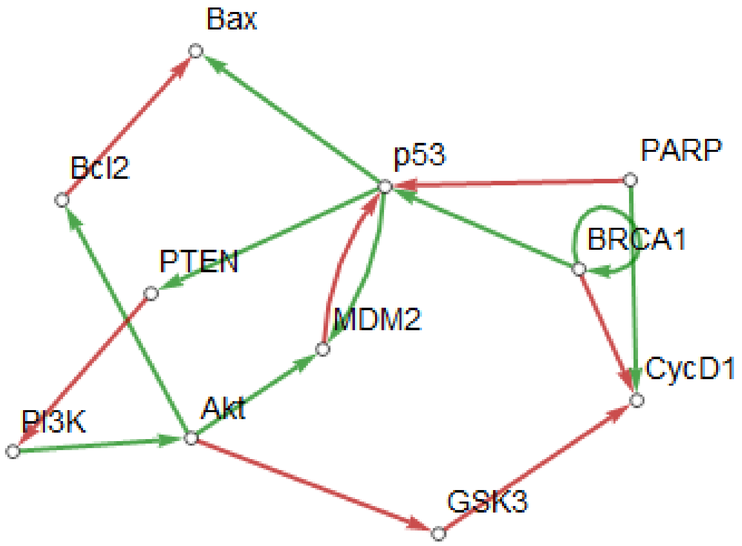


$$F_U = \begin{cases} x_1 = (x_2 \land u^0_{2,1}) \lor x_3 \\ x_2 = \neg\left(x_3 \lor \neg u^1_{3,2}\right) \\ x_3 = \left((\neg\, x_2 \land x_1) \lor \neg d^1_3\right) \land d^0_3 \end{cases}$$

Necessary Loss of 101 stable state

3 minimal solutions : Inhibit x3, Break x2-> x1,
(1,1,1,0),(0,1,1,1),(1,0,1,1) Break x3-> x2

Application to mutations prediction in Breast cancer



Freeze to False	Freeze to True
PTEN	Akt
P53	Bcl2
BRCA1	PI3K
GSK3	MDM2

Tumor supressors

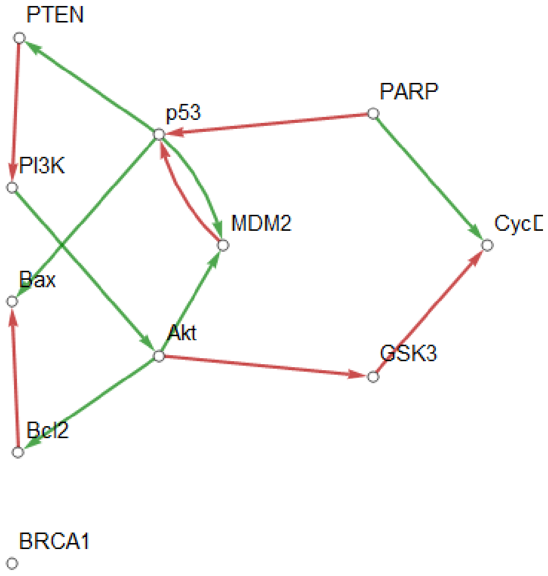
Oncogenes

Akt → PI3K
Bax → ¬ Bcl2 ∧ p53
Bcl2 → Akt
BRCA1 → BRCA1
CycD1 → ¬ GSK3 ∨ (¬ BRCA1 ∧ PARP)
GSK3 → ¬ Akt
MDM2 → Akt ∧ p53
p53 → ¬ MDM2 ∧ (BRCA1 ∨ ¬ PARP)
PARP → True
PI3K → ¬ PTEN
PTEN → p53

1) Actions on all nodes except markers

2) Necessary loss of apoptosis
→ Marking: CycD1=0, Bax=1

Application to drug targets prediction in Breast cancer



Akt → PI3K
Bax → ¬ Bcl2 ∧ p53
Bcl2 → Akt
BRCA1 → False
CycD1 → ¬ GSK3 ∨ (¬ BRCA1 ∧ PARP)
GSK3 → ¬ Akt
MDM2 → Akt ∧ p53
p53 → ¬ MDM2 ∧ (BRCA1 ∨ ¬ PARP)
PARP → True
PI3K → ¬ PTEN
PTEN → p53

1 Solution:
{PARP→p53, PARP→CycD1}

Olaparib drug action

1) Actions on Edges

2) Possible Gain of apoptosis
→ Marking: CycD1=0, Bax=1

Conclusion & Perspectives

- Cancer and drug targets can be found in molecular networks
- Dynamical systems reprogramming
- Control Boolean Network
- Algorithmic resolution of inference of control
- Library developped in Mathematica
- Application to the prediction of mutated genes in Breast Cancer and of their synthetic lethal partner

- Add weights to actions
- Application to the prediction of driver genes in Triple negative Breast Cancer

THANK YOU